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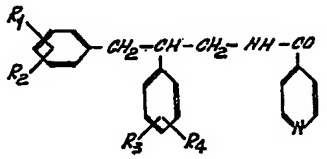
COMPLETE SPECIFICATION

Substituted Isonicotinic Acid Amides and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT vormals Meister Lucius & Brüning, a body corporate recognised under German law, of Frankfurt (Main)—Höchst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

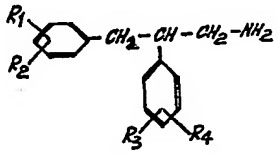
The present invention provides new substituted isonicotinic acid amides of the general formula



in which R_1 represents a halogen atom or a methyl or methoxy, R_2 and R_3 each represent a hydrogen or halogen atom, and R_4 represents a halogen atom.

The new compounds are valuable medicaments and have the special property of being capable of inhibiting the growth of tumors.

The invention also provides a process for the manufacture of the isonicotinic acid amides of the above formula, wherein a substituted 2:3-diphenyl-propylamine of the general formula



in which R_1, R_2, R_3 and R_4 have the meanings given above, is reacted with isonicotinic acid or a reactive derivative thereof.

As examples of amines used as starting materials in the process there may be mentioned: 2:3 - di - (4^1 - chlorophenyl)-propylamine, 2 - (4^1 - chlorophenyl) - 3-(3^{11}:4^{11} - dichlorophenyl) - propylamine, 2-(3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (2^{11}:4^{11} - dichlorophenyl)-propylamine, 2:3 - di - (3^1:4^1 - dichlorophenyl) - propylamine, 2 - (2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-fluorophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (4^{11} - bromophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-methoxyphenyl) - propylamine and 2-(2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - methylphenyl)-propylamine.

These amines may be obtained, for example, by reacting an appropriately substituted benzaldehyde or benzyl halide, in the presence of an alkaline condensing agent, with a substituted benzyl-cyanide, and then reducing the substituted α:β-diphenyl-acrylonitriles or α:β-diphenyl-propionitriles thus obtained, by a method in itself known.

The process may, for example, be carried out by reacting the hydrohalic acid salt of a reactive derivative, for example, a halide, of the isonicotinic acid such, for example, as isonicotinic acid chloride hydrochloride, in the presence of a basic compound, for example, a tertiary organic base such as pyridine, dimethyl aniline, triethylamine or an inorganic basically reacting salt such as potassium or sodium carbonate, and a solvent, with the substituted 2:3-diphenyl-propylamine. Advantageously the acid that is liberated is bound by means of pyridine, the latter being added in excess so that it is simultaneously used as solvent. The reaction is carried out at a normal or slightly below normal temperature.

In an alternative procedure an ester of isonicotinic acid, for example the ethyl ester thereof, is used as the reactive derivative. The reaction is then advantageously carried out by

mixing the isonicotinic acid ester with the amine and then heating the mixture at an elevated temperature, preferably at a temperature within the range of 180 to 250° C.

In a further alternative method isonicotinic acid is reacted with the substituted 2:3-diphenyl-propylamine by mixing, for example, equimolecular proportions of the acid and the amine and, completing the reaction, by heating the salt thus obtained for a short time in an open flask at an elevated temperature, preferably at a temperature within the range of 270—320° C., until no more water is split off.

Most of the new isonicotinic acid amides of this invention are colourless to yellowish solid compounds. Some of them can only be obtained as yellow, very viscous oils.

The compounds of the invention inhibit the growth of malignant tumors, and in this respect some of them are markedly superior to the known compounds of analogous structure. Apart from affording an absolutely higher *dosis tolerata* they have a higher chemotherapeutic index with respect to certain transplantation tumors than the known cytostatica. The isonicotinic acid 2-(3^1:4^1-dichlorophenyl)-3-(4^{11}-chlorophenyl)propylamide, for example, substantially inhibits the growth of tumors. This compound is effective, for example, in the case of a transplantable benzpyrene sarcoma of the golden hamster, whereas here the known cytostatica (ethylene imine derivatives, such as Thio-TEPA, TEM (registered Trade Mark), ethylene imine quinones and nitrogen mustard oxide) are completely ineffective. In the case of the transplantable benzpyrene sarcoma of the mouse, the compound is also more effective than the above mentioned known preparations.

The following Table I summarizes the test results of some products of the present invention and compares them with those obtained with thiophosphoric acid triethylene imide which is a cytostaticum known by the name of "Thio-TEPA":

TABLE I

Compound	(a)	(b)	(c)	Thio-TEPA
Dosis maxima tolerata per 20 g of mouse	100 mg subcutaneously, 25 mg per os	100 mg subcutaneously, 100 mg per os	50 mg subcutaneously, 30 mg per os	0.2 mg subcutaneously
Dosis therapeutica per 20 g of mouse	4×25 mg subcutaneously, 4×6.25 mg per os	4×25 mg subcutaneously, 4×25 mg per os	4×12.5 mg subcutaneously, 4×8 mg per os	4×0.05 mg subcutaneously
Tumours:				
solid Ehrlich carcinoma	+	+	(+) / +	(+) / +
sarcoma induced subcutaneously by means of methylcholanthrene	++/+++	++		++/+++
transplantable benzopyrene sarcoma of the golden hamster	(+) / +			no effect
dosis therapeutica per 100 g of the golden hamster	4×50 mg subcutaneously 4×12.5 mg per os			

(a) = isonicotinic acid-2-(3^1:4^1-dichlorophenyl)-3-(4^{11}-chlorophenyl)-*n*-propylamide

(b) = isonicotinic acid-2-(4^1-chlorophenyl)-3-(4^{11}-methoxyphenyl)-*n*-propylamide

(c) = isonicotinic acid-2:3-di-(4^1-chlorophenyl)-*n*-proplyamide

Each test result was determined by treating the tumor with the indicated dosis therapeutica of the particular product. The symbols used in the Table have the following meanings:

(+) means a 10—25% inhibition of the tumor as compared with the untreated controls.

+ means a 25—50% inhibition of the tumor as compared with the untreated controls.

+!+ means a 50—75% inhibition of the tumor as compared with the untreated controls.

+!+!+ means a 75—100% inhibition of the tumor as compared with the untreated controls.

The compounds of the invention may be used as such or as galenical preparations thereof, for example as tablets, capsules, dragees, ampoules, oily or aqueous solutions or suspensions or crystal suspensions, in admixture or conjunction with the usual pharmaceutical, organic or inorganic and physiologically tolerable carriers. As such carriers there are used those compounds which do not react with the compounds of the invention, for example water, gelatine, bolus, lactose, starch, magnesium stearate, talcum, tylose, vegetable oils such as olive oil, peanut oil, castor oil, cotton seed oil or neat's foot oil, or gum, propylene glycol, polyethylene glycol, zinc oxide or titanium dioxide. The compounds of the present invention or the corresponding galenical preparations thereof may be sterilized and/or may contain assistants such as stabilizers, buffers, wetting agents, emulsifiers or salts influencing the osmotic pressure. The galenicals are prepared by methods in themselves known. The compound of the invention may be added to the galenical preparation in a dosage of 0.1—10%. The human dosage is within the range of 0.2—2 grams per day.

The following Examples illustrate the invention:—

EXAMPLE 1.

Isonicotinic acid - [2:3 - di - (4^1 - chlorophenyl) - propyl] - amide

13.5 Grams of isonicotinic acid were heated with 28 grams of 2:3-di-(4^1-chlorophenyl)-propylamine in an open vessel for 5 minutes at 300—310° C. (bath temperature). Water was split off with effervescence. The still warm melt was dissolved in 30 cc of ethanol and then filtered. On cooling, 18.8 g of isonicotinic acid - [2:3 - di - (4^1 - chlorophenyl) - propyl] - amide melting at 126° C., crystallized.

EXAMPLE 2.

Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - fluorophenyl) - propyl] - amide

24.4 Grams of isonicotinic acid and 47 grams of 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-fluorophenyl)-propylamine were mixed and the mixture was heated in an open vessel for 5 minutes at 300—310° C. The still warm melt was dissolved in a little warm ethanol, and then filtered. About five times the quantity of diisopropyl ether was then added to the filtrate. 37 grams of crude isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11}-fluorophenyl)-propyl]-amide were obtained, and the product could be purified by dissolving in benzene and reprecipitating with petroleum ether. The compound melted at 115—116° C.

EXAMPLE 3.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide

33.5 Grams of isonicotinic acid and 78 grams of 2 - (3^1:4^1 - dichlorophenyl) - 3-(4^{11} - chlorophenyl) - propylamine were heated for 5 minutes in an open vessel at 300 to 310° C. The cooled melt was dissolved in 100 cc of ethanol on a steam bath, filtered and then water was added to the warm solution until it became turbid. After cooling and filtering the solution under suction, 66 grams of isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide were obtained.

The product was purified by recrystallization from ethanol/water. The pure compound was a colourless powder melting at 137—138° C.

EXAMPLE 4.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(2^1:4^1-dichlorophenyl)-propyl]-amide

27 Grams of isonicotinic acid and 62.9 grams of 2 - (4^1 - chlorophenyl) - 3-(2^{11}:4^{11} - dichlorophenyl) - propylamine were mixed and then heated in an open vessel for 5 minutes at 290—310° C. The cooled melt was dissolved in 100 cc of warm ethanol, filtered and the filtrate was mixed with 500 cc of diisopropyl ether. On standing in the refrigerator, the product crystallized. 64 grams of isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (2^{11}:4^{11} - dichlorophenyl)-propyl]-amide were thus obtained. The compounds could be purified by recrystallization from benzene. It then melted at 139—140° C.

EXAMPLE 5.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(4^{11}-methoxyphenyl)-propyl]-amide

27 Grams of isonicotinic acid and 55.1 grams of 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-methoxyphenyl)-propylamine were heated in an open vessel for 5 minutes at 300—310° C. The still warm melt was dissolved in a little ethanol, then filtered and the isonicotinic acid-[2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methoxyphenyl) - propyl] - amide was precipitated by addition of diisopropyl ether. The compound, which melted at 125° C., was obtained in a yield of 58 grams. The melting point was no different after recrystallization from benzene/petroleum ether.

EXAMPLE 6.

Isonicotinic acid - [2:3 - bis - (3^1:4^1 - dichlorophenyl)-propyl]-amide

13 Grams of isonicotinic acid and 35 grams of 2:3 - bis - (3^1:4^1 - dichlorophenyl)-propylamine were mixed and then heated in an open vessel for 10 minutes at 300—310° C. After cooling, the melt was dissolved in 150 cc of alcohol. The oil that separated after addition of a little water, solidified slowly on prolonged standing. After filtering under suction, 35 grams of a yellowish product were obtained. The isonicotinic acid-[2:3-bis-(3^1:4^1 - dichlorophenyl) - propyl]amide thus obtained could be purified by recrystallization from benzene/diisopropyl ether and then melted at 146—148° C.

By using 13 grams of isonicotinic acid and 28 grams of 2 - (4^1 - chlorophenyl) - 3-(2^{11}-chlorophenyl)-propylamine, and conducting the process in an analogous manner, 28 grams of isonicotinic acid-[2-(4^1-chlorophenyl) - 3 - (2^{11} - chlorophenyl) - propyl]-amide were obtained. After recrystallization from benzene/diisopropyl ether the product melted at 117—118° C.

EXAMPLE 7.

Isonicotinic acid - [2 - (2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide

13 Grams of isonicotinic acid and 31.5 grams of 2 - (2^1:4^1 - dichlorophenyl) - 3-(4^{11}-chlorophenyl)-propylamine were mixed and then heated for 5 to 10 minutes at 300—310° C. The cooled melt was dissolved in 150 cc of benzene and the undissolved material was removed by filtration. After adding a little petroleum ether, 26 grams of isonicotinic acid - [2 - (2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide crystallized out. By recrystallization from benzene/petroleum ether, a colourless powder melting at 117—118° C. was obtained.

EXAMPLE 8.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(3^{11}-chlorophenyl)-propyl]-amide

27 Grams of isonicotinic acid and 56 grams of 2 - (4^1 - chlorophenyl) - 3 - (3^{11} - chlorophenyl)-propylamine were mixed and then heated in an open vessel for 5 minutes at 300—310° C. The cooled melt was dissolved in chloroform, the solution was washed with dilute hydrochloric acid, then with a dilute sodium hydroxide solution and then with water, dried over sodium sulphate and finally distilled under reduced pressure. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (3^{11}-chlorophenyl) - propyl] - amide distilled at 305—310° C. under a pressure of 3 mm of mercury as a very viscous, yellow oil.

EXAMPLE 9.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(3^{11}:4^{11}-dichlorophenyl)-propyl]-amide

27 Grams of isonicotinic acid and 62.7 grams of 2 - (4^1 - chlorophenyl) - 3-(3^{11}:4^{11} - dichlorophenyl) - propylamine was heated for 5 minutes at 300—310° C. The cooled melt was dissolved in chloroform, washed with dilute hydrochloric acid, then with dilute sodium hydroxide solution and then with water, dried over sodium sulphate and, after evaporating the solvent, distilled under reduced pressure. 47 grams of isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3-(3^{11}:4^{11} - dichlorophenyl) - propyl] - amide boiling at 308—312° C. under a pressure of 2 mm Hg were obtained.

EXAMPLE 10.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - methoxyphenyl)-propyl]-amide

45 Grams of isonicotinic acid and 109 grams of 2 - (3^1:4^1 - dichlorophenyl) - 3-(4^{11} - methoxyphenyl) - propylamine were heated together for 10 minutes at 300 to 310° C. The cooled melt was dissolved in benzene, washed with water and then dried. On distillation of the reaction product, a very viscous, brown compound boiling at 315—320° C. under a pressure of 1.7 mm Hg was obtained in a yield of 77 grams.

EXAMPLE 11.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(4^{11}-bromophenyl)-propyl]-amide

A mixture of 14.5 grams of isonicotinic acid and 35 grams of 2-(4^1-chlorophenyl)-3-(4^{11} - bromophenyl) - propyl - amine was heated in an open vessel for 5 minutes at 290—300° C. The cooled melt was dissolved in 50 cc of ethanol. The product was crystallized by adding 500 cc of diisopropyl ether. 34 grams of isonicotinic acid-[2-(4^1-chlorophenyl) - 3 - (4^1 - bromophenyl) - propyl]-amide were obtained, and the product could be recrystallized from a mixture of ethyl acetate and diisopropyl ether (in a ratio of 1:2). The compound melted at 134—135° C.

EXAMPLE 12.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(4^{11}-methylphenyl)-propyl]-amide

27 Grams of isonicotinic acid and 52 grams of 2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methylphenyl)-propylamine were heated in an open vessel for 5 minutes at 300—310° C. The still warm melt was dissolved in 50 cc of ethanol. On cooling the solution, 55 grams of isnicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11}-methylphenyl) - propyl] - amide crystallized out. The compound could be purified by recrystallization from dilute ethanol and then melted at 133—134° C.

EXAMPLE 13.

Isonicotinic acid - [2:3 - di - (2^1:4^1 - dichlorophenyl)-propyl]-amide

34.9 Grams of 2:3-di-(2^1:4^1-dichlorophenyl)-propylamine and 13 grams of isonicotinic acid were heated together in an open vessel for 10 minutes at 300—310° C. The melt, which solidified on cooling to a glass

was taken up in ether, the ether solution was washed with water and then with a sodium bicarbonate solution, dried over sodium sulphate, and the solvent was then evaporated. On treating with petroleum ether the residue crystallized after standing for some days. Crystallization could be promoted by seeding. 30 grams of isonicotinic acid-[2:3-di-(2^1:4^1-di - chlorophenyl) - propyl] - amide were obtained as a yellowish compound that could be purified by recrystallization from acetonitrile and then melted at 128—130° C.

EXAMPLE 14.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide

63 Grams of 2 - (3^1:4^1 - dichlorophenyl)-3-(4^{11}-chloro-phenyl)-propylamine and 30.2 grams of isonicotinic acid ethyl ester were heated together in a flask that has an attached cooling tube, for 6 hours at 200—220° C. The cooled melt was dissolved in 50 cc of ethanol and then 500 cc of diisopropyl ether were added. 41 Grams of isonicotinic acid-[2 - (3^1:4^1 - dichloro - phenyl) - 3 - (4^{11}-chlorophenyl)-propyl]-amide crystallize out and, after recrystallization from ethanol/water, the compound melted at 138—139° C.

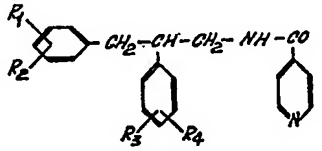
EXAMPLE 15.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide.

63 Grams of 2-(3^1:4^1-dichlorophenyl)-3-(4^{11} - chloro - phenyl) - propylamine were dissolved in 150 cc of pyridine and then 40 grams of isonicotinic acid chloride hydrochloride were added to the solution while cooling with ice. The mixture thus obtained was heated for 30 minutes on a steam bath and then poured into 4 litres of water, whereupon the product precipitated and solidified after some time. After filtering the product under suction, washing with water and air-drying 77 grams of isonicotinic acid-[2-(3^1:4^1 - dichlorophenyl) - 3 - (4^1 - dichlorophenyl)-propyl]-amide were obtained. After recrystallization from ethanol/water the compound melted at 138—139° C.

WHAT WE CLAIM IS:—

1. Substituted isonicotinic acid amides of the general formula



in which R_1 represents a halogen atom or a methyl or methoxy group, R_2 and R_3 each represent a hydrogen or halogen atom, and R_4 represents a halogen atom.

2. Isonicotinic acid - [2:3 - di - (4^1-chlorophenyl)-propyl]-amide.

3. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - fluorophenyl) - propyl]-amide.

4. Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl)-propyl]-amide.

5. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (2^{11}:4^{11} - dichlorophenyl)-propyl]-amide.

6. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methoxyphenyl) - propyl]-amide.

7. Isonicotinic acid - [2:3 - bis - (3^1:4^1-dichlorophenyl) - propyl] - amide.

8. Isonicotinic acid - [2 - 2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide.

9. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (3^{11} - chlorophenyl) - propyl]-amide.

10. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (3^{11}:4^{11} - dichlorophenyl)-propyl]-amide.

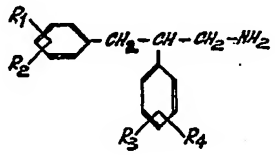
11. Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - methoxy - phenyl)-propyl]-amide.

12. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^1 - bromophenyl) - propyl]-amide.

13. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methylphenyl) - propyl]-amide.

14. Isonicotinic acid - [2:3 - di - (2^1:4^1-dichlorophenyl)-propyl]-amide.

15. A process for the manufacture of substituted isonicotinic acid amides of the general formula given in claim 1, wherein a substituted 2:3-diphenyl-propylamine of the general formula



in which R_1, R_2, R_3 and R_4 have the meaning given in claim 1 is reacted with isonicotinic acid or with a reactive derivatve thereof.

16. A process as claimed in claim 15, wherein the salt obtained by reacting isonicotinic acid with a 2:3-diphenyl-propylamine of the formula given in claim 15 is heated at a temperature within the range of 270—320° C., until no more water is split off.

17. A process as claimed in claim 15, wherein an isonicotinic acid ester is heated with a substituted 2:3-diphenyl-propylamine of the formula given in claim 15, at a temperature within the range of 180° C. and 250° C.

18. A pharmaceutical preparation which comprises a compound claimed in any one of claims 1—14 in admixture or conjunction with a pharmaceutically suitable carrier.

19. A process for the manufacture of isonicotinic acid amides of the general formula given in claim 1, conducted substantially as described in any one of the Examples herein.

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